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# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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17.06.2004  
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WRITTEN OPINION  
(PCT Rule 66)

ENTERED ONTO INPROMA

Date: 17/6/04 Initials: LG

Date of mailing  
(day/month/year)

15.06.2004

Applicant's or agent's file reference  
WPP286385

REPLY DUE

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International application No.  
PCT/GB 03/03327

International filing date (day/month/year)  
30.07.2003

Priority date (day/month/year)  
30.07.2002

International Patent Classification (IPC) or both national classification and IPC  
C07D407/06

Applicant  
PHARMA MAR, S.A.U. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
  - I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

**If no reply is filed**, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 30.11.2004

Name and mailing address of the international preliminary examining authority:



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**I. Basis of the opinion**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

**Description, Pages**

1-112 as originally filed

**Claims, Numbers**

1-49 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 24

because:

☒ the said international application, or the said claims Nos. 24 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	
Inventive step (IS)	Claims	1,23,38
Industrial applicability (IA)	Claims	

2. Citations and explanations

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 24 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**Novelty**

The present application relates to myriaporones analogues and their use as medicaments for the treatment of cancer. Myriaporones are natural polyketide- derived products isolated from the bryozoan *Myriapora truncata*. The present application represents an attempt at the total synthesis of myriaporones and derivatives according to genera formula (I) with the proviso that the natural compounds described in D1 are excluded.

The synthetic route involves i.a. removing a protecting group from a compound of formula **5a** wherein at least one group R is a protecting group to give the corresponding compound of formula **5b** where the said at least one group R is hydrogen and preferable at least one of the R substituents is not hydrogen.

According to schemes 1 as well as 2 the same method of producing compounds of formula I is shown whereby according to scheme 2, a different stereochemistry in the oxazolidinone 9 (which is R in scheme 1 and S in scheme 2) or oxazolidinone 21.

None document of the cited prior art describes a total synthetic route for the production of myriaporones. Novelty can be thus acknowledged.

**Inventive step**

The problem underlying the present application appears to reside in the provision of myriaporone analogues via an efficient, stereo controlled total synthetic route for their production.

D1 only describes fractionation and purification of active components from the methanol extract of the bryozoan *Myriapora truncata*. Among those metabolites isolated, compounds MT-332 (compounds 3 and 4) and compound MT-381 and MT-381-B (compounds 1 and 2 respectively) are the ones which exhibit pronounced

cytotoxicity.

D2, which has been referred to by the applicant in the description page 1, relates to the asymmetric preparation of a potential intermediate in the total synthesis of myriaporones. However a lack of stereoselectivity has been observed.

According to the other documents cited only C(x)-C(y) segments of the whole natural product(s) were synthesised which each represented a progress toward the total synthesis of myriaporones.

The problem has been solved by the synthetic route providing compounds of general formula (I).

Data are given in terms of yields, achievement of the desired stereochemistry as well as inhibition of cell growth the latter obtained from different human cancer types.

However before a favourable IPER can be issued, Applicant's attention is drawn to the following remarks:

- a) the Examiner wishes to point out that terms such as "alkyl, alkynyl, aryl or heteroaryl being optionally further substituted" used i.a. in claim 1, are considered to be non-limitative and embrace an infinite number of possibilities not yet explored by the Applicant; they should therefore be limited to the specific meanings given in the description as otherwise it will be difficult to ascertain if the problem has been indeed solved by all the compounds claimed considered as obvious modifications or equivalents to one or more particular examples.
- b) The reference to D1 at the end of claim 1 should be avoided and replaced by the compounds names (eg "... that the compound is not the natural compound designated as MT332 or MT 381...").
- c) "Prodrug"- Protection cannot be sought for speculative compounds, which have yet to be prepared and investigated. There is no specific indication within the application as to what may be a prodrug, nor is a prodrug a definable term as regards the structure of such a compound. The skilled person has no indication as to what falls within this definition, and it should thus be deleted.

#### Industrial applicability

The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for

the manufacture of a medicament for a new medical treatment.